REMARKS

Entry of this amendment and reconsideration of the rejection of the claims is respectfully requested.

Claims 57, 69, 114, and 106 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications. Claims 1-54, 102, and 115-120 were previously cancelled without prejudice or disclaimer. These claims were previously subject to a restriction requirement.

Claims 55, 58, 63, 64, 70-72, 99, 105 and 107-110 are currently amended to clarify the subject matter of the claims. Claims 58, 70,71, 72, and 107-110 are amended to provide antecedent basis or change dependencies from a cancelled claim. These amendments are supported throughout the specification including at page 4, lines 28 to 36.

Claims 121-132 are new and are supported throughout the specification including at page 5, line 35 to page 6, line 25, page 34, lines 30-35, and page 35, lines 19-30.

No new matter is introduced by these amendments.

Restriction

The Examiner indicated that claims 86 and 100 have been withdrawn from consideration as being drawn to nonelected inventions. Applicants agree that claim 86 was withdrawn from examination due to species election requirement between single and separate polynucleotides. Applicants request rejoinder of the claim and examination if the elected species is found allowable.

The remaining claims, including claim 100, remain under examination. Claim 100 recites a single polynucleotide that encodes both DsbA and DsbC. The claim does not conflict with any restriction or species election requirement previously indicated by the Examiner. Reinstatement of claim 100 is respectfully requested.

IDS Acknowledgement

Applicants thank the Examiner for acknowledging and considering IDSs filed on 07/14/2006 and 10/27/2006.

Objections to the Claims

Claims 63, 64 and 99 were objected to for informalities. Specifically, the Examiner objected to the recitation of the acronyms DsbA, DsbC and DsbG.

Applicants submit that the term "Dsb" is an acronym for the phrase disulfide bond formation, and is so recognized by those of skill in the art. *See, e.g.*, Kurokawa et al., *J. Biol. Chem.* 276(17): 14393-14399 (2001). However, without acquiescing in the objection, and solely in the interest of expediting allowance, claim 63, 64 and 99 have been amended to recite the expanded form of "Dsb." Withdrawal of the objections is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 55, 57–85, 87–99, 101 and 103–114 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

Specifically, the Examiner contends that the specification fails to disclose a sufficient number of species to support the term "polynucleotide" as broadly encompassed by the present claims. The Examiner further contends that written description is only present for cDNAs corresponding to the particular antibodies disclosed in the Examples (i.e. anti-tissue factor antibody and anti-VEGF antibody). Applicants respectfully disagree with this contention.

There is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim,* 191 USPQ 90, 97 (C.C.P.A 1976). The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Id.* at 97. Compliance with the written description requirement does not require an applicant to

describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow,* 217 USPQ 1089 (Fed. Cir. 1991).

Claim 55 is directed to an isolated polynucleotide comprising a polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue forms an inter-chain disulfide linkage when present. Claim 66 is directed to a method of producing an intact antibody comprising expressing in a prokaryotic host cell the polynucleotide of claim 55, wherein the amount of intact antibody produced from the host cell is increased in comparison to the amount of aggregated heavy chain produced in the host cell, and recovering said intact antibody from the host cell. Claim 105 provides a method for producing an intact antibody comprising: expressing in a prokaryotic host cell a polynucleotide comprising a polynucleotide encoding a variant immunoglobulin heavy chain; wherein said variant immunoglobulin heavy chain comprises a hinge region in which at least one cysteine is modified, wherein the at least one cysteine residue forms an inter-chain disulfide linkage when present and when modified no longer forms a disulfide linkage, and wherein said variant immunoglobulin heavy chain comprises a reduced ability to form a disulfide linkage such that amount of self aggregation of the variant immunoglobulin heavy chain is less than the amount of self aggregation of a reference immunoglobulin heavy chain when expressed under similar conditions, wherein the reference immunoglobulin heavy chain has a wild type ability to form a disulfide linkage.

Contrary to the Examiner's assertion, the claimed "polynucleotide encoding an antibody" is not any nucleic acid, modified nucleotide or bases that can be incorporated into a polymer by DNA or RNA polymerase. Applicants submit that relevant, identifying

characteristics of the polynucleotide are provided in the specification. The specification states that cysteine residues in the heavy chain hinge regions play a role in heavy chain aggregation (*see* page 64, ll. 28–30). The specification exemplifies that when one or more of these cysteine residues were converted to serine residues, aggregation of the heavy chain was reduced, and yield of intact antibodies were improved. The present claims now are directed to an isolated polynucleotide that encodes for an intact antibody comprising a variant heavy chain comprising a variant hinge region that does not form inter-heavy chain linkages and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue forms an inter-chain disulfide linkage when present. The structure and sequence of hinge regions and cysteine residue present in the hinge region are known to those of skill in the art. Thus, Applicants submit that the disclosure is sufficient to allow a person of ordinary skill in the art to determine the structure of the polynucleotide that encodes the antibody in the claims, and to determine applicants were in possession of the claimed subject matter. Therefore, the written description requirement is met.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

Claims 55, 57–85, 87–99, 101 and 103–114 were rejected under 35 U.S.C. § 102(b) as anticipated by Gillies et al., *Human Antibody Hybridomas* 1: 47–54 (1990), and by Davis et al., *EMBO J.* 9: 2519–2526 (1989). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Because neither Gillies nor Davis teach each and every element of the claims, they do not anticipate the claimed subject matter.

Gillies does not teach an isolated polynucleotide comprising a polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy

chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue forms an inter-chain disulfide linkage when present, methods for producing intact antibodies, or for reducing aggregation of an immunoglobulin heavy chain. Gillies et al teaches a construct only encoding the heavy chain variable domain, the CH1 domain and an altered hinge region and does not teach an intact antibody. Therefore, as Gillies fails to teach each and every element of the present claims, the reference does not anticipate the present claims.

The Examiner contends that Davis teaches methods of making IgM variants by replacing cysteine residues involved in forming inter-heavy chain disulfide bonds. Applicants submit that Davis fails to disclose an isolated polynucleotide that encodes an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages. In fact, Davis makes no mention of cysteine residues present in the hinge region of a variant heavy chain. In fact, it is known in the art that IgM lacks a hinge region (*see, e.g.*, page 29, ll. 16 of the present Application). Therefore, as Davis fails to teach each and every element of the present claims, the reference does not anticipate the present claims.

Based on the foregoing, withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

Claims 55, 57–85, 87–99, 101 and 103–114 were rejected under 35 U.S.C. § 102(b) as anticipated by Simmons et al. (U.S. Patent Pub. No. 2005/0170464). Applicants respectfully traverse this rejection.

The present claims are directed to isolated polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue

forms an inter-chain disulfide linkage when present and methods for producing intact antibodies and reducing aggregation of .

The Simmons reference is directed to methods for improved expression and production of biologically active antibodies by using separate cistrons under the control of separate promoters and including separate translation initiation regions. The reference indicates that a cysteine residue not involved in maintaining the proper conformation of the antibody can be substituted by serine residue. The Simmons et al reference, states "The capability of a full length antibody to exert one or more of its natural activities depends on several factors, including proper folding and assembly of the polypeptide chains. As used herein, the biologically active immunoglobulins generated by the disclosed methods are typically heterotetramers having two identical L chains and two identical H chains that are linked by multiple disulfide bonds and properly folded." See para[0049]. At para[0103], the Simmons et al reference states "Sufficient disulfide bonds are particularly important for the formation and folding of full length, bivalent antibodies having two heavy chains and two light chains." Therefore, the Simmons et al reference does not teach or suggest that an intact antibody can or should be produced wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein said variant hinge region lacks a cysteine residue, wherein the cysteine residue forms an inter-chain disulfide linkage when present. Further, the Simmons et al reference does not discuss aggregation of heavy chains or that alteration of hinge region cysteines can affect the amount of aggregation and increase the yield of intact antibodies. Therefore, as the Simmons reference does not disclose each and every element of the present claims, the claims are not anticipated. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 55, 57–85, 87–99, 101 and 103–114 were rejected under 35 U.S.C. § 103(a) as unpatentable over Gillies et al. and Davis et al., in view of Georgiou et al. (U.S.

Patent No. 5,264,365) and Kurokawa et al., *J. Biol. Chem.* 276: 14393–14399 (2001). Applicants respectfully traverse the rejection.

To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* A dependent claim is not obvious if the claim from which it depends is not obvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). The initial burden to make a *prima facie* case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993). Applicants submit that the Examiner does not make a *prima facie* case of obviousness, because all the limitations of the present claims are not taught by the combination of references cited in the Office Action.

Applicants initially note that the following discussion of the references cited by the Examiner is not meant to attack the references individually. The references are discussed individually only to show that the combination asserted by the Examiner fails to teach all the limitations of the present claims. The present claims are directed to an isolated polynucleotide comprising a polynucleotide that encodes an intact antibody comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region which does not form inter-heavy chain disulfide linkages, and wherein the variant hinge region lacks a cysteine residue, wherein the cysteine residue forms an inter-chain disulfide linkage when present..

The arguments and remarks provided above with respect to the Gillies and Davis references are also fully relevant here and are incorporated by reference to avoid repetition. To briefly summarize, Gillies fails to teach or suggest an isolated polynucleotide comprising a polynucleotide encoding an intact antibody as recited in the present claims. Davis fails to teach or suggest substitution of hinge region cysteine residues, since IgM does not have hinge region. Georgiou is directed to construction of protease deficient *E. coli* hosts used to produce proteolytically sensitive peptides. Kurokawa describes product of NGF in *E. coli*, and the effect of Dsb protein overexpression on NGF production. None of these references, when combined, teach or suggest a polynucleotide comprising a polynucleotide encoding an intact antibody

comprising a variant heavy chain, wherein the variant heavy chain comprises a variant hinge region that does not form inter-heavy chain disulfide linkages.

Moreover, there is no motivation to combine the cited references. Gillies is focused on antibody fragments or mutant antibody constructs and the interaction of effector functions and antigen binding of these mutant constructs. Gillies does not discuss whether these mutant antibody constructs affect heavy chain aggregation or can increase antibody production. In fact, expression of the antibody constructs as described by Gillies et al shows formation of a heavy chain dimer. See figure 5. Thus, one of ordinary skill in the art would not be led to use the constructs of Gillies to decrease heavy chain aggregation.

Davis describes assembly of IgM subunits and makes no mention of disulfide linkages formed by hinge region cysteine residues. In fact, a person of skill in the art would know that IgM subunits have no hinge cysteines, and therefore, would not be motivated to combine the reference with the other references cited by the Examiner. Georgiou is directed to protease-deficient *E. coli* host cells. Kurokawa is directed to enhancing disulfide bond formation in *E. coli*, and therefore teaches away from polynucleotides encoding antibodies where disulfide bond formation is prevented by mutation of cysteine residues in the hinge region. A person of skill in the art would not be motivated to combine these references to arrive at the isolated polynucleotides or methods of the present claims. A *prima facie* case of obviousness has not been made.

In view of the remarks above, the rejection under 35 U.S.C. § 103(a) is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

INTERVIEW REQUEST

Applicants request an interview with the Examiner and her supervisor upon receipt of these papers.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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